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Circadian Genes and Risk for Prostate Cancer

PRINCIPAL INVESTIGATOR:
Ann W. Hsing, PhD

CONTRACTING ORGANIZATION:

TRUE Research Foundation

San Antonio, TX 78217

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13. SUPPLEMENTARY NOTES

14. ABSTRACT: We propose that genetic susceptibility to prostate cancer may be in part due to variations in the core circadian genes that regulate circadian rhythms and that serum sex steroid hormone levels modify the effect of circadian gene polymorphisms on prostate cancer risk. Our study is nested within the Prostate Cancer Prevention Trial (PCPT), a randomized placebo-controlled clinical trial to determine if finasteride (an inhibitor of androgen bioactivation) could prevent prostate cancer. In Year 2 of the award, we were approved by the DoD to changed our contracting genotyping facility to the University of Texas Health Science Center at San Antonio (UTHSCSA), which was mandated by the PCPT executive committee, and have been involved in analyzing serum androgen data that will be used for Aim 2 of our study. We have been working with the UTHSCSA to ensure that the genotyping assays for our study using the new genotyping platform will be successful. We have also had the DNA samples re-plated at the PCPT biorepository and shipped to UTHSCSA for genotyping.

15. SUBJECT TERMS
Prostate cancer, circadian genes, genetic susceptibility

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Table of Contents

INTRODUCTION: **Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.**

Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer death in men in the United States yet the only established risk factors for prostate cancer are race, age, and family history [1]. Recent data from observational studies on sleep duration [2], light at night [3], rotating shift workers [4, 5], and male airline pilots [6-8] suggest that circadian rhythm disruptions increase prostate cancer risk; no underlying molecular mechanism has yet been identified. We propose that genetic susceptibility to prostate cancer may be in part due to variations in genes from a number of pathways including the core circadian genes that regulate circadian rhythms. The goal of this project is to test the novel hypothesis that variants in circadian genes alter the risk of prostate cancer and that serum sex steroid hormone levels modify the effect of circadian polymorphisms on prostate cancer risk. Our study is nested within the Prostate Cancer Prevention Trial (PCPT), a randomized placebo-controlled clinical trial to determine if finasteride (an inhibitor of androgen bioactivation) could prevent prostate cancer. Included in our study are approximately 1,800 case-control pairs (3,600 individuals), for which several biological measurements are available, including serum sex hormone levels, which we will also incorporate into our study to test our hypothesis.

BODY: **This section of the report shall describe the research accomplishments associated with each task outlined in the approved Statement of Work. Data presentation shall be comprehensive in providing a complete record of the research findings for the period of the report. Provide data explaining the relationship of the most recent findings with that of previously reported findings. Appended publications and/or presentations may be substituted for detailed descriptions of methodology but must be referenced in the body of the report. If applicable, for each task outlined in the Statement of Work, reference appended publications and/or presentations for details of result findings and tables and/or figures. The report shall include negative as well as positive findings. Include problems in accomplishing any of the tasks. Statistical tests of significance shall be applied to all data whenever possible. Figures and graphs referenced in the text may be embedded in the text or appended. Figures and graphs can also be referenced in the text and appended to a publication. Recommended changes or future work to better address the research topic may also be included, although changes to the original Statement of Work must be approved by the Army Contracting Officer Representative. This approval must be obtained prior to initiating any change to the original Statement of Work.**

Our study has three specific aims, all of which utilizes genotyping data that is to be generated in Award Years 1-2. The second year of the award involved tasks as outlined in the Statement of Work. The following is a report as it pertains to each task in Award Year 2:

Task 1 Data management
Performance sites: NCI and PCPT Statistical Center
Performance period: Months 1-36 (entire period)

We have been in constant communications with the PCPT Statistical Center at the Fred Hutchinson Cancer Research Center (Seattle, WA) since the project's inception. Genotyping data for this project will be incorporated into the PCPT central database as are data from serum androgen assays (completed as part of a separate study but will be used for Aim 2 of this study). With the PCPT Statistical Center, we have completed the analysis on pre- and post-

treatment serum androgen levels and prostate cancer risk (supported by a different mechanism). The data on serum androgens and results from the analysis will be used to help guide the analysis for Aim 2 of the study.

Task 2 Develop and perform genotyping assays on 320 SNPs (including 40 putatively functional and 270 tag SNPs as well as additional SNPs to account for control SNPs and potential SNP assay failures) of circadian genes in approximately 4,000 samples including 1,800 case-control pairs (3,600 subjects) and approximately 400 duplicate quality control samples.
Performance sites: University of Texas Health Science Center at San Antonio (UTHSCSA) [changed from Roswell Park Cancer Institute (RPCI) Microarray and Genomics Facility.]
Method: Illumina BeadXpress Genotyping Platform
Performance period: Months 1-24
Anticipated Outcome: Genotyping results on approximately 320 SNPs for 3,600 subjects.

During the first half of Award Year 2, the PCPT Executive Committee recommended that and subsequently mandated for all genotyping assays for all PCPT sub-studies be performed at the University of Texas Health Science Center at San Antonio (UTHSCSA). This decision was due to the more efficient genotyping platform that was implemented at the UTHSCSA genotyping core facility. We submitted the revision to Task 2 to our DoD contracting officer when the PCPT Executive Committee informed us of their decision and were subsequently given approval for the change in our study. Because of this change, Additional QC work has to be performed before genotyping can begin. First, the DNA samples had to be reconfigured and re-plated to accommodate the new genotyping platform; the DNAs have recently been shipped to UTHSCSA. And second, we had to work with UTHSCSA to ensure that the new genotyping platform will still allow us to genotype the SNPs included in our study. It is anticipated that the genotyping will be completed during the first half of Award Year 3.

Task 3 Monitor quality of genotyping results on an ongoing basis
Performance sites: NCI, PCPT Statistical Center
Method: Analyses of Hardy-Weinberg equilibrium, inter-individual genotype call rates, concordance of duplicate specimens or known controls, and other quality control (QC) measures.
Performance period: Months 7-36

As mentioned above for Task 2, there was a change in genotyping facility (and platform) as mandated by the PCPT Executive Committee. DoD approved this change, and we have been working with UTHSCSA to ensure that the new genotyping platform will allow us to genotype the SNPs included in our study.

Task 4 Gather, ship, process, and archive biospecimens
Performance sites: University of Texas Health Science Center at San Antonio (UTHSCSA) [changed from Roswell Park Cancer Institute (RPCI) Microarray and Genomics Facility.]
Performance period: Months 1-20

Because of the change in genotype facility, the DNA samples were reconfigured and re-plated to accommodate the new genotyping platform. The DNAs have recently been shipped to UTHSCSA.

Task 5 Prepare hormone data from PCPT
Performance sites: PCPT Statistical Center
Method: Assay results of serum hormone analysis as part of the PCPT Program Project will be submitted to the PCPT database by mid-2008; integration of the data will be handled by the PCPT Statistical Center; request for access to data will be requested for the performance period.
Performance period: Months 13-20

We have been working with the PCPT Statistical Center on analyzing data related to serum androgen levels as part of the PCPT Program Project; these data were submitted to the PCPT database in mid-2009 and integrated into the PCPT database. Dr. Ann Hsing, the PI of the current award, is leading the analysis and two manuscripts describing the results are in preparation. These data will help guide data analysis necessary to complete Aim 2 of the current study.

Tasks 6 Perform statistical analysis and *Task 7 Prepare scientific presentations & manuscripts:*

These tasks have been delayed due to the change in genotyping facility as described under Task 2.

KEY RESEARCH ACCOMPLISHMENTS: Bulleted list of key research accomplishments emanating from this research.

- None for the reporting period

REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this research to include: manuscripts, abstracts, presentations; patents and licenses applied for and/or issued; degrees obtained that are supported by this award; development of cell lines, tissue or serum repositories; informatics such as databases and animal models, etc.; funding applied for based on work supported by this award; employment or research opportunities applied for and/or received based on experience/training supported by this award.

There are currently no reportable outcomes from this project.

CONCLUSION: Summarize the results to include the importance and/or implications of the completed research and when necessary, recommend changes on future work to better address the problem. A "so what section" which evaluates the knowledge as a scientific or medical product shall also be included in the conclusion of the report.

The goal of this project is to test the novel hypothesis that variants in circadian genes alter the risk of prostate cancer and that serum sex steroid hormone levels modify the effect of circadian polymorphisms on prostate cancer risk. In Year 2 of the award, we were approved by the DoD to changed our contracting genotyping facility to the University of Texas Health Science Center at San Antonio (UTHSCSA), which was mandated by the PCPT executive committee, and have been involved in analyzing serum androgen data that will be used for Aim 2 of our study. We have been working with the UTHSCSA to ensure that the genotyping assays for our study using the new genotyping platform will be successful. We have also had the DNA samples re-plated at the PCPT biorepository and shipped to UTHSCSA for genotyping.

REFERENCES: **List all references pertinent to the report using a standard journal format (i.e. format used in *Science, Military Medicine*, etc.).**

1 Hsing AW, Chokkalingam AP. Prostate cancer epidemiology. Front Biosci 2006;11:1388-413.

2 Kakizaki M, Inoue K, Kuriyama S, et al. Sleep duration and the risk of prostate cancer: the Ohsaki Cohort Study. Br J Cancer 2008;99:176-8.

3 Kloog I, Haim A, Stevens RG, et al. Global Co-Distribution of Light at Night (LAN) and Cancers of Prostate, Colon, and Lung in Men. Chronobiol Int 2009;26:108 - 25.

4 Kubo T, Ozasa K, Mikami K, et al. Prospective cohort study of the risk of prostate cancer among rotating-shift workers: findings from the Japan Collaborative Cohort Study. Am J Epidemiol 2006;164:549-55.

5 Conlon M, Lightfoot N, Kreiger N. Rotating shift work and risk of prostate cancer. Epidemiology 2007;18:182-3.

6 Band PR, Le ND, Fang R, et al. Cohort study of Air Canada pilots: mortality, cancer incidence, and leukemia risk. Am J Epidemiol 1996;143:137-43.

7 Irvine D, Davies DM. British Airways flightdeck mortality study, 1950-1992. Aviat Space Environ Med 1999;70:548-55.

8 Pukkala E, Aspholm R, Auvinen A, et al. Cancer incidence among 10,211 airline pilots: a Nordic study. Aviation, space, and environmental medicine 2003;74:699-706.

APPENDICES: **Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.**

None

SUPPORTING DATA: **All figures and/or tables shall include legends and be clearly marked with figure/table numbers.**

None.